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**DETAILED DESCRIPTION**

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**[Detailed Description of the Invention]****[0001]**

**[Field of the Invention]**This invention relates to the cartridge incorporated and used for the active immunity measuring device which quantifies automatically the minor constituent which exists in a sample.

**[0002]**

**[Description of the Prior Art]**By quantifying the minor constituent in body fluid, such as human blood, various specific selective reactions are used from the former in the so-called field of the diagnostic drug which it is going to utilize for sick diagnosis and therapy. Such a specific selective reaction makes body fluid, such as blood, a sample, and aims at measuring the quantity of minor constituents, such as a disease marker which exists in this.

For example, an antigen-antibody reaction etc. are mentioned.

What is called immunoassay etc. are performed by using such an antigen-antibody reaction.

**[0003]**The measuring method which used the immune agglutination also in such immunoassay is used widely as a measuring method with simple operation. Substances (an antibody or an antigen) in which this measuring method has specific selective reaction nature to the measuring object in a sample, and immunonephelometry from which a measuring object produces an aggregate directly, By making the surface of the carrier like a latex microparticle support the substance which has specific selective reaction nature to the measuring object in a sample, and contacting the liquid which contains this particle after an appropriate time, and sample liquid, There is latex agglutination which produces and cheats out of a specific selective reaction, and produces an aggregate, and all measure the absorbance which changes with aggregates.

**[0004]**In recent years, improvement in this field progresses and the automatic measuring instrument which performs all the processes of immunoassay automatically prospers now.

**[0005]**The active immunity measuring method by the solid phase technique performed in JP,63-281053,A using the container which has two or more wells, such as a reaction well which has a fibrous matrix, and sample wells, is indicated. However, in this method, the device which supplies a reagent required for immunoassay other than the cartridge to be used was indispensable, it was needed and there was a problem which changes a supply reagent with change of the substance used as a measuring object and to which the composition of the device for automation becomes complicated.

**[0006]**The active immunity measuring method using the container which has two or more openings and with which one of the openings has solid phase at least is indicated by JP,4-218775,A. However, this art is

related with the art in which solid phase is a magnetic particle essentially, and flexibility has a scarce fault, and also operativity was not necessarily a good thing.

[0007]In JP,11-316226,A, it has a reaction vessel which reacts, and two or more storing tubs with which the reagent was filled up, and the cartridge which makes solution form all the reagents required for the inside of a storing tub and with which it is filled up is indicated including the antibody sensitization carrier used for enzyme-labeling immunoassay or radioimmunoassay. However, although this cartridge has pack-sized all the reagents, only a penetrant remover is supplied from the outside.

Operativity was not necessarily good.

[0008]Each conventional method is the immunoassay using the container which has two or more wells, and aims at automation of measurement. However, since these methods did not hold some reagents required for measurement in a container or did not hold them at all, apart from a container, the reagent required for measurement needed to be prepared separately and there were problems, like the composition of a device becomes complicated in automation.

[0009]

[Problem(s) to be Solved by the Invention]Then, this invention is a cartridge for including in an automatic measuring instrument in view of the above. The purpose is to provide the cartridge which can measure simple with completeness 1 cartridge type per one sample.

[0010]

[Means for Solving the Problem]This invention is a thing, and said reaction vessel has said immunological substance in the inside, and said two or more storing tubs, A reaction vessel which is characterized by that a cartridge being what fills up the inside with all the reagents required for said immunoreaction independently comprises the following and which performs immunoreaction, A cartridge incorporated and used for an automatic measuring instrument which quantifies automatically a minor constituent which has two or more storing tubs for being filled up with a reagent used for said immunoreaction, and exists in a sample. Immunoreaction which performs said automatical measurement using an immunological substance which has special reactivity with a minor constituent in said sample.

Optical measurement to an aggregate based on this immunoreaction.

This invention is explained in full detail below.

[0011]

[Embodiment of the Invention]This invention is a cartridge incorporated and used for the automatic measuring instrument which quantifies automatically the minor constituent which exists in a sample. Especially if the shape of the above-mentioned whole cartridge has a reaction vessel and two or more storing tubs, it will not be limited, for example, the brake-shoe type thing etc. in which a reaction vessel and two or more storing tubs are located in a line in parallel, and exist are mentioned (refer to drawing 1).

[0012]Although the size in particular of the above-mentioned cartridge is not limited, in order to incorporate and use for an automatic measuring instrument, a smaller thing is preferred, for example, what is 1-10 cm in length, 0.5-5 cm in height, and about 0.3-3 cm in thickness is mentioned.

[0013]Especially if the sizes and shape of the above-mentioned reaction vessel and two or more storing tubs are the well-like things which can perform storing of a reaction which is mentioned later, and a reagent, they

will not be limited, but a cylindrical thing about 1-10 mm in diameter, a rectangular parallelepiped type thing, etc. are preferred, for example. As these dig the above-mentioned cartridge, they can constitute it. The shape of the well itself may be cylindrical, or a prismatic form may be sufficient, the bottom may be circular or corniform may be sufficient as it. In this invention, in order to observe optically the specific reaction which advances in a well from the outside of a well, it is desirable to form the cartridge portion applicable to at least a part of side of this well by the light transmittance state substance.

[0014]Although the well currently formed by the above-mentioned light transmittance state substance is equivalent to the photometry cell in optical measurement, it may serve as it by two or more storing tubs with which the reagent is filled up before use.

[0015]In order to avoid mixing of a foreign matter, the reaction vessel and storing tub of the above-mentioned cartridge, It is preferred to carry out the seal of the upper part, and what pasted up aluminium foil, a high polymer film, etc. on the cartridge upper surface with hot melt adhesive, for example is mentioned as such a seal, for example. The seal by aluminium foil can be easily broken with the seal breaker etc. with which the automatic measuring instrument was equipped, and is preferred from sealing performance being good.

[0016]Although not limited by the substance which checks the specific reaction performed in a reaction vessel as a raw material of the above-mentioned cartridge, especially removing that there is nothing, things etc. which have cheap and easy shaping, such as polystyrene resin, polyethylene resin, and polypropylene resin, are mentioned, for example. For example, it can make it possible to measure an absorbance with a part optical altimeter directly in case of transparent polystyrene resin.

[0017]The abandonment tub for discarding the fluid (waste fluid) by which it is generated when a series of reactions and measurement are completed can be provided. By providing such an abandonment tub, measuring work can be rearranged easily. Among two or more above-mentioned storing tubs, during measuring work, an abandonment tub may divert the storing tub which becomes empty, and, of course, may provide it independently.

[0018]The cartridge of this invention may have a mechanism which docks the cuvette containing sample liquid. Usually, the cuvette container with which the sample liquid which pretreatment of centrifugal separation etc. ended went into the automatic measuring instrument apart from the cartridge is also set. Then, a measuring device extracts sample liquid from a specimen container, and offers it to a reaction within a cartridge. If it has a mechanism like this invention, the space in an automatic measuring instrument can be used effectively and the miniaturization of a device can be expected.

[0019]With the above-mentioned sample, body fluid, such as human blood, etc. are mentioned, for example. By measuring the minor constituent in a sample in fixed quantity immunologically, it can use for human sick diagnosis and therapy, and a disease marker [ say / for example, / a hepatitis virus, a rheumatoid factor, C-reactive protein, a hemolytic-streptococcus toxin, various enzymes, etc. ] is mentioned.

[0020]Now, the cartridge of this invention produces and cheats out of an aggregate by exciting immunoreaction in the inside, and the minor constituent in a sample is measured by reading the optical change to the aggregate.

[0021]As the above-mentioned immunological substance, especially if it has specific immune response nature with the above-mentioned minor constituent, it will not be limited, For example, the antibody etc. of the minor constituent illustrated above may be mentioned, and these antibodies may be monoclonal

antibodies, or may be polyclonal antibodies, and may be the decomposition products of an antibody further. [0022]The immunological substance can choose suitably the case where a carrier is not needed, and the case where it is supported by the carrier and a reaction is presented. When using a carrier, in this invention, the above-mentioned carrier exists in the inside of the above-mentioned reaction vessel. It is preferred that it is a solid, it is a particle-like bead more preferably, and the above-mentioned carrier is a still more desirable latex bead made from polystyrene (the carrier which supported the above-mentioned immunological substance hereafter may be called as a sensitization carrier). When an immunological substance is made to support to up to a carrier, the carriers concerned are made to condense by carrying out the specific reaction which made the immunoagglutination method the principle.

[0023]As a size of the above-mentioned latex microparticle used as a carrier, it is used widely by an immunoagglutination method, for example, the latex microparticle with a mean particle diameter of 0.01-5 micrometers which carried out the graft copolymerization of the polyethylene to polystyrene is preferred, and is 0.1-0.7 micrometer in diameter more preferably.

[0024]It is not limited especially as a method of making the above-mentioned latex microparticle supporting the above-mentioned immunological substance (sensitization is carried out), for example, a publicly known physical-adsorption method or a chemical bond method can be used conventionally.

[0025]Independently, all the required reagents make solution form two or more storing tubs of the cartridge of this invention about immunonephelometry, and the inside is filled up with them. Saying describe above "become independent", every one each of two or more storing tubs may be filled up with the separate reagent, one storing tub may be filled up with two or more reagents, and it means that the storing tub with which it does not fill up further at all may exist. With "solution form", some reagents have packed as a freeze-drying article, and being solution-ized with the buffer solution etc. with which it similarly fills up is also included at the time of use.

[0026]Then, two or more above-mentioned storing tubs are filled up with all the reagents required for a specific selective reaction and a reaction with a marker, and the gist of this invention is at the point that a series of immunoreaction can be completed only with the reagent which exists in the above-mentioned storing tub.

[0027]Thus, the futility of a reagent is lost by cartridge-izing and the necessity of preparing a reagent whenever a measuring object is changed is also lost. Namely, what is necessary is just to determine the cartridge to be used, and at the same time it determines measuring object material like the cartridge for C-reactive protein, and the cartridge for rheumatoid factors. Since a cartridge can be produced independently and can be applied for every measuring object material, the measurement misconception based on reagent confusion becomes that there is nothing.

[0028]Of course, it is also possible to measure two or more items simultaneously by enclosing independently the reagent the object for C-reactive protein measurement and for rheumatoid factor measurement with each of two or more storing tubs in one cartridge, for example. In that case, what is necessary is to write in the arithmetic circuit by the side of an automatic measuring instrument, to make it freedom, and just to enable it to change a measurement sequence free.

[0029]Sample liquid is introduced into the reaction vessel of the cartridge of this invention by a suitable method. For example, after introducing a sample by the technique directly to the cartridge of this invention, cuvette may be set in a measuring device, the cuvette containing sample liquid may be set to the device

side, and the cuvette by which sample liquid went into the cartridge of this invention may be made to dock like point \*\*. The above-mentioned sample liquid is human blood etc. as already mentioned above.

[0030]In the above-mentioned reaction vessel, the minor constituent which exists in the above-mentioned sample liquid produces immunoreaction by touching the carrier (latex bead) which supported the above-mentioned immunological substance or the above-mentioned immunological substance. By producing immunoreaction, the condensation between beads is started, for example and optical measurement can be presented.

[0031]In order to advance the above-mentioned immunoreaction good, it is preferred to introduce the buffer solution for a latex bead etc. being suspended in the above-mentioned reaction vessel besides the above-mentioned sample liquid. You make it filled up with the above-mentioned buffer solution in the above-mentioned storing tub as a reagent required for a reaction in this invention. Especially as the above-mentioned buffer solution, it is not limited, the buffer solution usually used for an antigen-antibody reaction etc. can be used, for example, a cow serum albumin content phosphate buffer solution etc. are mentioned 0.1%.

[0032]When making a whole blood sample besides the above-mentioned buffer solution for suspension into a sample, it can also be filled up with the buffer solution containing a hemolyzing agent for destroying a corpuscle component (in order to distinguish from the buffer solution for latex suspension, a diluent may be called below) in a storing tub. As a kind of hemolyzing agent, saponin can use it preferably.

[0033]When making a whole blood sample into a sample, a possibility of producing an error in a measurement result for the hemoglobin contained in red corpuscles is high. Therefore, the storing tub filled up with the reagent for measuring a fixed quantity of hemoglobin can be prepared, a hematocrit value can be computed using the hemoglobin concentration obtained by computing hemoglobin concentration simultaneously with the time of sample measurement, and sample measured value can also be amended.

[0034]After the above-mentioned specific selective reaction is completed and optical measurement is completed, the remains mixture of the above-mentioned sample liquid and the above-mentioned buffer solution is eliminated as waste fluid out of a reaction vessel by an aspirator etc., for example. Waste fluid is discarded by the abandonment tub like point \*\*.

[0035]In this invention, the reagent (two or more kinds) with which it is filled up in the above-mentioned storing tub is solution form, respectively. Since it is considered as solution form, the introduction to a reaction vessel from a storing tub can carry out simple by the single operation by a pipette.

[0036]In order that suction and the pipette for carrying out the regurgitation may prevent contamination for a solution, it is preferred to wash the inside of a pipette with a penetrant remover etc. About this penetrant remover, it is possible to consider it as the embodiment dedicated to one place of the cartridges of this invention, and it is considered as the feature of this invention.

[0037]The penetrant remover needed for the work for washing the unreacted components in immunoassay, and what is called B/F separation, It is made usual to be supplied from some devices of an automatic measuring instrument, without dedicating in a cartridge, since a lot of things are usual and it is a substance which does not need to be changed according to the kind of minor constituent used as a measuring object.

[0038]However, the cartridge of this invention is an object for immune agglutination, and B/F separation is not needed for the immune agglutination. Therefore, a lot of penetrant removers were not needed, but it succeeded in stopping a penetrant remover in a cartridge by specializing only in the penetrant remover for

pipette washing.

[0039]Especially if the above-mentioned immune agglutination is not affected as the above-mentioned penetrant remover, it will not be limited, for example, a physiological saline, deionized water, etc. are mentioned.

[0040]In this invention, when putting each liquid reagent of the above-mentioned latex suspension, the diluent for hemolysis, and a penetrant remover into a storing tub, it is preferred to fill up another storing tub with each.

[0041]Although the number of the above-mentioned storing tubs can be suitably decided by the number, the operativity, and simple nature of a solution form reagent, it is usually 3-8 pieces more preferably 2-10 pieces. As an example of restoration to each storing tub, it is shown in drawing 2. It can also be used in order to dilute the place and sample which prepare an empty storing tub and put in the sample to measure as shown in a figure.

[0042]

[Example]With reference to drawings, this invention is explained in detail below. Drawing 2 is an example which shows the composition of the cartridge of this invention. The cartridge which is used in carrying out this invention has a cell (A, B, C) and a well (1-6). A cell is a reaction vessel for measuring the strength of the light, and a well means a storing tub.

[0043]It is a tub which includes the disposable pipette tip for doing pipetting work before [ other than these cell wells ] cartridge use, and after use has a tub which turns into an abandonment tub.

[0044]It has the cuvette for setting to a cartridge the sample tub used when a user pours in a sample directly to a cartridge, and the sample included in a general-purpose small tube etc. the whole tube. The sample tub of cartridge attachment and the change between sample tubes are arbitrary, and it can attain easily by directing sequence change to the device side.

[0045]In front of use of a cartridge, a sample tub, the well 1, cell ABC, and an abandonment tub are empty. the hemoglobin determination reagent for performing hemoglobin amendment to the well 2 -- the well 3 -- the diluent for hemolysis (saponin content physiological saline) -- a chip penetrant remover (distilled water) is carried out at the well 5, and restoration enclosure of the latex suspension is carried out for buffer solution at the well 6 at the well 4, respectively. Since a reagent kind changes with items, the physical relationship of an excessive cell well changes.

[0046]If the whole blood which is a sample is poured in to the sample tub of a cartridge and a cartridge is set in a device, the following measurement procedures will be performed automatically.

[0047]By a tip part with a sharp pipette nozzle of the seal breaker combination in a device, after the lamination seal of a cartridge is broken, the pipette tip included by the cartridge docks with the pipette nozzle by the side of a device.

[0048]Next, distributive pouring of 95mulx2 physiological salines and a total of 190microl is performed by pipette operation from the well 3 to the well 1.

[0049]Next, 84micro of buffer solution is poured distributively 1 times from the well 4 in the cell B.

[0050]Next, a hemoglobin determination reagent is performed by distributive pouring of a total of 154microl 77micro twice [ lx ] from the well 2 in the cell A.

[0051]Next, after the suction regurgitation of 110microl is performed twice by the physiological saline which remained in the well 3, a chip is washed by transporting distilled water 50mul of the well 5 to an

abandonment tub.

[0052]Next, 10micro of samples I of a sample tub are poured distributively by the well 1, and a 5 times line crack, and stirring, mixing and dilution are performed for the suction regurgitation in 110microl.

[0053]After the suction regurgitation of 110microl is performed twice by the physiological saline which remained in the well 3, a chip is washed by transporting distilled water 50mul of the well 5 to an abandonment tub.

[0054]Next, 28micro of dilution samples I of the well 1 are poured distributively by the cell A, and the suction regurgitation in 110microl is performed 5 times, and is stirred and mixed. An absorbance variation is detected at this time and hemoglobin concentration is measured. A hematocrit value is computed from the obtained hemoglobin concentration.

[0055]On the other hand, after the suction regurgitation of 110microl is performed twice by the buffer solution which remained in the well 4, a chip is washed by transporting distilled water 50mul of the well 5 to an abandonment tub.

[0056]Next, 48micro of dilution samples I of the well 1 are poured distributively by the cell B, and the suction regurgitation in 85microl is performed 5 times, and is stirred and mixed. After the suction regurgitation of 110microl is performed twice by the distilled water which remained in the well 5, a chip is washed by transporting distilled water 110mul of the well 5 to an abandonment tub.

[0057]Next, latex liquid 28.2mul of the well 6 is poured distributively by the cell B, and the suction regurgitation in 110microl is performed 3 times, and is stirred and mixed. An absorbance variation is detected at this time and the target constituent concentration is measured.

[0058]At the end, amendment of the hematocrit value acquired simultaneously to the obtained constituent concentration and constituent concentration is performed.

[0059]It is possible to enforce the measuring method which measures a sample continuously by automating each operation explained above by the device side. The composition of the method and device which automate pipette operation by the device side can be freely changed according to the purpose of measurement, the shape of a cartridge, etc., and there is no restriction in particular.

[0060]

[Effect of the Invention]Since the reagent also including a penetrant remover required for measurement is enclosed with one cartridge according to this invention, It is easy to carry out automation of measurement by a device, and can respond altogether by one cartridge to one measuring object material, therefore the futility of a reagent is lost, reagent management becomes very simple and easy, and the simple and quick measurement of it is attained, and it carries out a big contribution to the field of a clinical laboratory test.

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[Translation done.]

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**CLAIMS**

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**[Claim(s)]**

[Claim 1]A cartridge incorporated and used for an automatic measuring instrument which quantifies automatically a minor constituent which has a reaction vessel characterized by comprising the following which performs immunoreaction, and two or more storing tubs for being filled up with a reagent used for said immunoreaction, and exists in a sample.

Immunoreaction which performs said automatical measurement using an immunological substance which has special reactivity with a minor constituent in said sample.

Optical measurement to an aggregate based on this immunoreaction.

[Claim 2]A cartridge given in the 1st paragraph of a range of an application for patent into which all the required reagents are filled up with solution form.

[Claim 3]A cartridge given in the 1st paragraph of a range of an application for patent which some required reagents are filled up with a freeze-drying article, and is returned to solution form at the time of use.

[Claim 4]A cartridge given in the 1st paragraph of a claim, wherein said two or more storing tubs serve as a photometry cell for optical measurement.

[Claim 5]A cartridge given in the claim 1st or the 4th paragraph which has an abandonment tub for discarding waste fluid which a reaction ended.

[Claim 6]A cartridge given in the 5th paragraph of a claim that is that to which an abandonment tub diverts a used storing tub.

[Claim 7]A cartridge given in the 1st paragraph of a claim that can dock cuvette containing a sample.

[Claim 8]A cartridge given in the 1st paragraph of a claim with which said immunological substance is supported by carrier surface.

[Claim 9]A cartridge given in the 8th paragraph of a range of an application for patent whose carrier is a latex microparticle 0.1-0.7 micrometer in diameter.

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